# Modified Simultaneous Integrated Boost Radiotherapy for Unresectable Locally Advanced Breast Cancer: Preliminary Results of a Prospective Clinical Trial☆

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## Abstract

**Unresectable massive T4 breast tumor cannot be controlled by radiotherapy of ≤70Gy. Modified SIB irradiation technique enables to irradiate ≥100Gy to the tumor, keeping dose to the surrounding healthy tissue within tolerance dose. Huge tumors of all 3 patients enrolled in the clinical trial macroscopically disappeared by modified SIB radiotherapy.**

**Background:** The purpose of this study was to evaluate the effect of modified simultaneous integrated boost (SIB) radiotherapy for patients with extensive breast cancer. **Patients and Methods:** Patients with macroscopic tumor and histologically proven adenocarcinoma of the breast were enrolled in the study. Patients were included whether they had or did not have previous surgery, chemotherapy, hormone therapy, or molecular targeted therapy; patients with past history of thoracic radiotherapy were excluded. Under conditions of not exceeding the tolerance dose for normal tissue, irradiation to the tumor was increased to the maximum possible extent using the modified SIB technique. **Results:** Three breast cancer patients were treated with the modified SIB technique. All patients were diagnosed as T4b (median maximum diameter of the tumor: 16 cm; range, 15.5-22 cm), and all patients exhibited symptoms because of the extremely large tumor. The median total dose to the part of tumor tissue was 128.8 Gy (range, 110-140 Gy). Total dose to normal tissue was $< 72$ Gy in all patients. Although large tumors were radioresistant, it was macroscopically confirmed that all tumors eventually disappeared. Although skin defects persisted because of tumor disappearance, there were no Grade $\geq 3$ toxicities due to radiotherapy. **Conclusion:** Although much care is required in delivering extremely high doses of radiotherapy to the tumor, modified SIB radiotherapy was shown to be effective against extremely large tumors that could not be controlled using conventional radiotherapy. In future, an increase in the number of study patients and establishment of the technique will be required.

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## Introduction

The incidence of advanced breast cancer is 80-120 per 1,000,000 people.[1,2] For patients with locally advanced breast cancer, chemotherapy, radiotherapy (RT), and hormone therapy are mainly performed when the tumor is deemed unresectable.[3,4] The primary drugs used for induction chemotherapy are as follows: anthracycline



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(doxorubicin), taxanes (paclitaxel and docetaxel), cyclophosphamide, 5-fluorouracil, and so on.

In some cases, curative surgery and postoperative RT are performed for good responders to induction chemotherapy; in other cases, chemotherapy (and/or RT) is performed for nonresponders to induction chemotherapy.[2] However, a standard treatment for locally advanced breast cancer (eg, large T4 tumor) has yet to be established. In this study, we used a new irradiation technique for advanced breast cancer patients, and report the efficacy and feasibility of this new approach.

## Patients and Methods

### *Patients*

Our investigation was designed as a prospective study of modified simultaneous integrated boost (SIB) RT for far-advanced cancer. The primary end point was defined as local response (rate of complete response and partial response); secondary end points were defined as toxicity, quality of life (QOL), and overall survival rate. Histologically proven breast cancer patients with large ($\geq$ 10 cm) and unresectable tumors were enrolled in the study. Patients were enrolled in the study regardless of the presence or absence of previous surgery, chemotherapy, and/or hormone therapy. Patients with untreated advanced breast cancer, recurrent breast cancer, and treatment-resistant breast cancer were also included in the study. However, patients with a past history of thoracic RT were excluded. Patients aged 20 years or older were included, as were patients with a performance status of 0 to 4. Written informed consent was obtained from all enrolled patients. This study was been approved by the institutional review board (H22-97).

### *Radiotherapy*

Four- to 10-MV photon and 4- to 20-megaelectron volt (MeV) electron beams from a high-energy linear accelerator were used for treatment. Irradiation was performed once a day with 5 fractions per week. Immobilization devices were used as necessary. Skin markers and image guidance (using flat panel detector) were used in the setup process. Irradiation was performed under shallow breathing without respiratory gating. Computed tomography-based RT planning was performed using XiO (Elekta Inc, Tokyo, Japan), and dose distribution was calculated using a superposition algorithm. The macroscopic tumor was defined as gross target/tumor volume (GTV), and metastatic lesion was also regarded as GTV. The subclinical region (10 mm) around GTV and level I to III axillary lymph node (LN) area (and supraclavicular LN area if there was LN metastasis) was defined as clinical target volume (CTV). The target volume, including CTV and setup margins of 5 to 10 mm, was defined as planning target volume (PTV).

### *Modified SIB Technique*

The standard SIB technique involves irradiating CTV with a prophylactic dose and GTV with a curative dose. For example, RT with standard SIB is used for head and neck tumors with regional LN metastasis. The technique enables a prophylactic dose of radiation to be delivered to the LN region with higher doses to the primary tumor and metastatic lesion.[5-7] Because a complex dose

**Table 1** Patient Characteristics

| Patient | Age, Years | Sex | TNM | Stage | Primary Lesion | Histology | History of Chemotherapy | Tumor Diameter (Maximum) | Metastasis | Symptoms |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 62 | F | T4bN2M0 | IIIb | Right breast | IDC (solid-tubular) | Weekly PTX x4 (courses), FEC x5, 3 Weekly DOC x3 (PD) | 15.5 cm | AxLN | Skin ulcer, pain, bleeding |
| 2 | 48 | F | T4bN3M1 | IV | Left breast | IDC (solid-tubular) | FEC x3, DOC x3, TS-1 daily (PD) | 16 cm | AxLN, lung, liver | Skin ulcer, pain, edema |
| 3 | 58 | F | T4bN1M1 | IV | Left breast | IDC (scirrhous) | FEC x2, Weekly PTX with HER x4, VNB with HER x1 (PD) | 22 cm | ScLN | Skin ulcer, pain, edema, bleeding |

Abbreviations: AxLN = ipsilateral axillary lymph node(s); DOC = docetaxel; F = female; FEC = 5-fluorouracil, epirubicin, and cyclophosphamide; HER = Herceptin (trastuzumab); IDC = invasive ductal carcinoma; PTX = paclitaxel; ScLN = supraclavicular lymph node(s); TNM = tumor, node, metastases; TS-1 = tegafur-gimeracil-oteracil potassium; VNB = vinorelbine.

**Table 2** Details of the Radiotherapy

| Patient | RT Number | Target | Modality | Voltage (MV/MeV) | Fields, n | Total Dose | Dose per Fraction | Frs | Treatment Schedule (Days From the Start) | Total Dose (Part of the Tumor) | Total Dose (Normal Tissue) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 1 | BR and LN (part) | E | 12 | 1 | 20 Gy | 4 Gy | 5 | 1-7 | | |
| | 2 | BR and LN | X | 4 | 2 | 30 Gy | 2 Gy | 15 | 8-28 | | |
| | 3 | BR and LN | X | 4 | 2 | 20 Gy | 2 Gy | 10 | 29-43 | | |
| | 3' | BR and LN (part) | E | 6 | 1 | 20 Gy | 2 Gy | 10 | 29-43 | | |
| | 4 | BR and LN | X | 4 and 10 | 2 | 20 Gy | 2 Gy | 10 | 44-58 | | |
| | | | | | | | | | | 110 Gy | 70 Gy |
| **2** | 1 | BR (part) | E | 12 | 1 | 20 Gy | 4 Gy | 5 | 1-7 | | |
| | 1' | LN (part) | E | 16 | 1 | 20 Gy | 4 Gy | 5 | 1-7 | | |
| | 2 | BR and LN | X | 4 | 2 | 50 Gy | 2 Gy | 25 | 14-52 | | |
| | 2' | BR (part) | E | 12 | 1 | 50 Gy | 2 Gy | 25 | 14-52 | | |
| | 2'' | LN (part) | E | 16 | 1 | 50 Gy | 2 Gy | 25 | 14-52 | | |
| | 3 | BR and LN | X | 4 | 2 | 10 Gy | 2 Gy | 5 | 55-59 | | |
| | 3' | Left BR (part) | E | 6 | 1 | 10 Gy | 2 Gy | 5 | 55-59 | | |
| | 3'' | LN (part) | E | 9 | 1 | 10 Gy | 2 Gy | 5 | 55-59 | | |
| | | | | | | | | | | 140 Gy | 60 Gy |
| **3** | 1 | BR | X | 10 | 2 | 28 Gy | 2 Gy | 14 | 1-21 | | |
| | 1' | BR (part) | X | 10 | 2 | 30.8 Gy | 2.2 Gy | 14 | 1-21 | | |
| | 2 | BR | X | 10 | 2 | 14 Gy | 2 Gy | 7 | 22-32 | | |
| | 2' | BR (part) | X | 10 | 2 | 14 Gy | 2 Gy | 7 | 22-32 | | |
| | 3 | BR | X | 4 and 6 | 3 | 20 Gy | 2 Gy | 10 | 33-45 | | |
| | 4 | BR | X | 4 | 2 | 10 Gy | 2 Gy | 5 | 47-54 | | |
| | 5 | BR (part) | E | 6 | 1 | 10 Gy | 2 Gy | 5 | 56-63 | | |
| | | | | | | | | | | 128.8 Gy | 72 Gy |

The RTs of the same number were performed simultaneously (modified simultaneous integrated boost technique). "Part" means irradiation to the part of the tumor without irradiation to normal tissues.
Abbreviations: BR = breast tumor; E = electron beam; LN = lymph node metastasis; MeV = mega-electron-volt; RT = radiotherapy; X = x-ray.

distribution is required, RT with standard SIB usually involves intensity-modulated RT (IMRT).

In this study, normal tissue tolerance dose limits were strictly followed; the dose to GTV was increased as much as possible without exceeding tolerance dose. Upper limits of total dose of normal thoracic tissues were defined as follows (in 2-Gy per fraction): skin, 60 Gy $\leq$ 30 $cm^2$, 70 Gy $\leq$ 10 $cm^2$, 80 Gy $\leq$ 1 $cm^2$; ipsilateral lung, 45 Gy $\leq$ 1/3 volume, 70 Gy $\leq$ 1 $cm^3$; heart, 45 Gy $\leq$ 2/3 volume, 60 Gy $\leq$ 1/3 volume; rib, 66 Gy $\leq$ 1/3 volume (for necrosis, not for fracture); spinal cord, 50 Gy $\leq$ 1 cm, 46 Gy $\leq$ 10 cm; and fat/muscle, 80 Gy $\leq$ 1 $cm^3$.[8-10]

Maximum dose to GTV was not defined, and heterogeneity in the dose distribution of GTV was allowed. For RT planning in this study, we used 3-dimensional conformal radiation therapy and IMRT. An equivalent dose in 2 Gy per fraction ($EQD_{2Gy}$) was calculated using the following formula: $EQD_{2Gy} = (\text{total dose}) \times (\text{dose per fraction} + \alpha/\beta)/(2 + \alpha/\beta)$.[11] If there were no annotations, a simple cumulative dose was described.

### *Other Treatments and Evaluations*

Chemotherapy, hormone therapy, and molecular targeted treatments during RT were permitted. Anticancer drug regimens were not restricted. The toxicity of the treatment was evaluated according to the Common Terminology Criteria of Adverse Events, version 4.0.[12] Each symptom of the patients was evaluated from subjective and objective findings using a numerical rating scale from 0 (normal or absence of symptoms) to 10 (worst possible or unbearable pain). Patients received a physical examination weekly during the RT treatment period, and received a physical examination monthly after the completion of RT treatment.

## Results

Until March 2012, 3 patients with locally advanced breast cancer were referred for RT, and all 3 patients were treated using RT and the modified SIB technique. Patient characteristics are shown in Table 1. The 3 patients were diagnosed with adenocarcinoma (invasive ductal carcinoma). Chemotherapy regimens, FEC (5-fluorouracil, epirubicin, and cyclophosphamide), taxanes (paclitaxel or docetaxel), and/or Herceptin (trastuzumab) were initiated for all 3 patients because there was no indication for surgery. However, all 3 patients were eventually categorized with progressive disease, and were therefore introduced to the department of radiation oncology. All patients had extremely large tumors of > 15 cm with symptoms of cancer pain, skin ulcer, oozing, edema, and so on. The patients' schedules and RT parameters are shown in Table 2. Day 1 in Table 2 is defined as the first day of RT, and RT described with the same number indicates the same schedule. For example, RT 3 and 3' of patient 1 were performed on the same schedule; therefore, 4 Gy per fraction per day was given to part of the breast tumor and metastatic tumors in this series of treatments.

**Figure 1** Radiotherapy (RT) Planning for Patient 2. (A) Initial Treatment for Axillary Lymph Node Metastasis (RT No. 1', E-16 MeV, 20 Gy/5 Fractions/1 Week). (B) The Second Treatment (RT No. 2 and No. 2''). Gross Target/Tumor Volume (GTV) and Clinical Target Volume Were Included in the 2-Gy Area, With Additional Irradiation of 2 Gy to the Part of GTV (2 Gy + 2 Gy = 4 Gy/Fraction Is Irradiated With the Modified Simultaneous Integrated Boost [SIB] Technique). (C) The Third Treatment (RT No. 3). Although Only RT No. 3 Is Displayed, There Were Additional Fields (RT No. 3' and No. 3'') Using Manual Planning With the Modified SIB Technique. (D) The Approximate Dose Distribution Derived From the RT Plans Using the Modified SIB Technique. The Total Dose to the Part of GTV Reaches 140 Gy (Simple Cumulative Dose), but the Total Dose to Normal Tissue Does Not Exceed Tolerance Dose

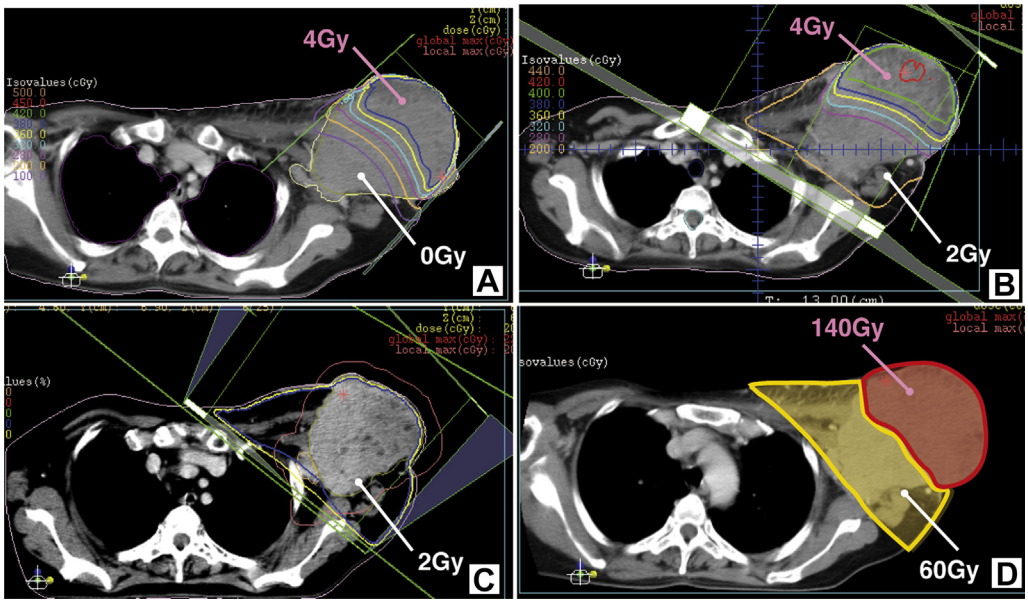
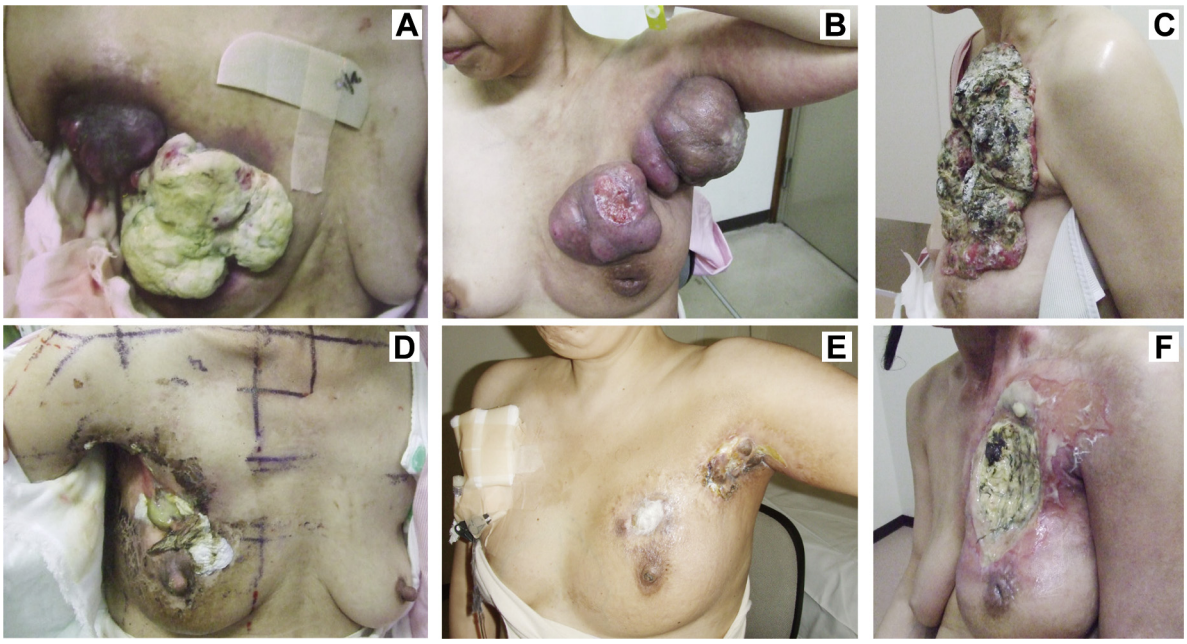


**Figure 2** Macroscopic Findings for Patients 1, 2, and 3. (A) Patient 1 Before Radiotherapy (RT). (D) Patient 1 After RT (Day 80). The Skin Defect Was Shrinking at That Time. (B) Patient 2 Before RT. (E) Patient 2 After RT (Day 142). The Skin Defect Has Almost Disappeared. (C) Patient 3 Before RT. (F) Patient 3 After RT (Day 90). Although a Large Skin Defect Remained, Regeneration of the Surrounding Normal Tissue Has Been Observed



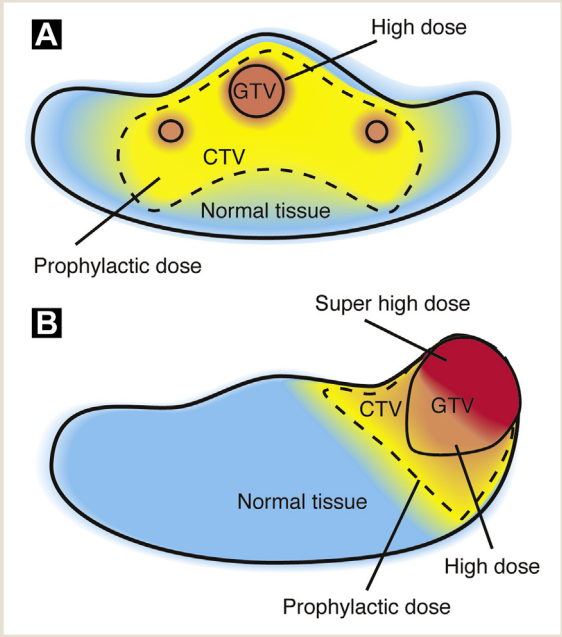

The RT plans for patient 2 are shown in Figure 1. Figure 1A shows the RT for metastatic LNs (this RT and another RT for the breast tumor do not overlap). Figure 1B shows the RT for metastatic LNs using the modified SIB technique (sum of RT 2 and 2"). Figure 1C shows RT 3 of patient 2 (RT 3' and 3" were manually planned and combined). Figure 1D shows the approximate dose distribution for the sum of all RT plans for patient 2. Although the total dose (cumulative dose) to the part of the tumor exceeds 140 Gy, the total dose to the normal tissues (axilla or chest wall) was 60 to 70 Gy. Assuming $\alpha/\beta$ of the tumor was 10, a 2-Gy equivalent dose to the part of GTV was calculated as 163 Gy, whereas the dose to the normal tissues was almost the same (60-70 Gy). Regarding the other 2 patients, total doses to the part of the tumor and the normal tissue were 110 Gy and 70 Gy in patient 1 and 128.8 Gy and 72 Gy in patient 3. The $EQD_{2Gy}$ to the part of GTV in patient 1 and patient 3 were calculated as 120 Gy and 143 Gy, respectively.

Radiotherapy for these patients was accomplished within 58 to 63 days. There was no treatment delay due to toxicity. Scheduled treatments were fulfilled for all of the patients. Figure 2 shows the photos of the 3 patients before RT (Figure 2A-C) and after RT (Figure 2D-F). Figure 2D, E, and F show day 80 of patient 1, Day 142 of patient 2, and Day 90 of patient 3, respectively. The median time to tumor disappearance was 90 days from the start of RT. Although much time was required, irradiated tumors disappeared macroscopically in all patients.

Local cancer pain was relieved in all patients. Considering skin ulceration in all 3 patients, the skin defect area was reduced in patient 1 and skin defect caused by tumor almost disappeared in patient 2. The largest skin defect caused by tumor in patient 3 was greatly reduced, but did not disappear (Figure 2D-F). Arm edema in 2 patients improved with a reduction in tumor volume. Tumor odor also diminished with a reduction in tumor volume. The main toxicity from RT was radiation dermatitis of Grade $\leq 2$. Skin defect after tumor disappearance was not considered to be treatment toxicity because it was deemed a complication of the tumor. There were no other definite toxicities from RT using the modified SIB technique. The 3 patients died 5 months, 5 months, and 8 months, respectively, after the start of RT. All 3 patients developed (or had developed) distant metastases. Two patients died from metastatic progression, whereas the third died from uncontrolled bleeding from the skin defect where the tumor existed. For these 3 patients, the cause of death was categorized as cancer-related.

The major symptoms of these patients were pain, hemorrhage, odor, and edema (arm). There were fewer changes in each symptom in the first 2 to 3 weeks from the start of RT. However, the score of each symptom improved as the treatment progressed. Pain relief tended to appear early after the start of irradiation, whereas the improvement of edema tended to appear late after the start of irradiation. The patients were able to discontinue the treatment if they felt pain in continuing the treatment, and the patients confirmed whether or not they wanted to continue the treatment every week during the treatment. All of the patients actively wished to continue the scheduled treatment, and there was no request from any of the patients to discontinue the treatment.

**Figure 3** (A) The Concept of Standard Simultaneous Integrated Boost (SIB) Radiotherapy. The Whole Clinical Target Volume (CTV) Is Irradiated With a Prophylactic Dose, Whereas Gross Target/Tumor Volume (GTV) Is Irradiated With a Higher Curative Dose. Generally, Dose Distribution in GTV Is Uniform. (B) The Concept of Modified SIB Radiotherapy in the Present Study. The Whole CTV Is Irradiated With a Prophylactic Dose. Further, a Part of GTV Is Irradiated With an Extremely High Dose Using Additional Field. However, Irradiation to the Normal Tissue Does Not Exceed the Tolerance Dose. Because Normal Tissue Does Not Exist Outside GTV (Normal Tissue Has Already Been Lost to the Tumor), Radiation Injury Will Not Occur Even If Irradiated by > 100 Gy




## Discussion

Because the required dose to control the tumor increases as the size of the tumor increases,[13-15] the control probability of adenocarcinoma of more than 10 cm is extremely low with a normal tissue tolerance dose.

In this study, using a new RT technique the giant tumor was irradiated with > 100 Gy without exceeding the tolerance dose to the normal tissue. A conventional concept of RT recommends a homogeneous dose distribution in PTV. Contrary to conventional concept, an SIB method that can alter dose intensity according to site has recently been reported.[5-7] This technique enables irradiation at a prophylactic dose to CTV and a higher (curative) dose to GTV, simultaneously. However, dose distribution to GTV is uniform in this standard SIB technique (Figure 3A).

Compared with standard SIB methodology, the modified SIB technique in this study delivered an extremely high dose to the part of GTV without exceeding the normal tissue tolerance dose (Figure 3B). Because of the priority that irradiation to normal tissue does not exceed tolerance levels, dose distribution to GTV is not always uniform. This is the pivotal difference between the general and the modified SIB techniques in the current study. The control probability of the extremely high-dose area in GTV will significantly increase, which is the same as the tumor volume being reduced by half. Based on the evidence that tumor volume and the required irradiation dose correlate, volume reduction of the tumor will increase local control probability. However, because sufficient CTV/PTV margins would increase the risk of toxicity of the surrounding normal tissues, unnecessary margins should be cut from the simultaneous boost irradiation field to protect such tissue (Figure 1A and B: electron beam).

### *Response/Clinical Course*

The tumor of patient 2 (Figure 2B) seemed to be radio-resistant, and almost no response was observed at the end of RT (Day 55). However, the tumors shrunk remarkably at day 94, and almost disappeared. Skin defects also almost disappeared at 3 months after RT (Figure 2E). Adenocarcinoma is radio-resistant compared with squamous cell carcinoma, and the response to irradiation of adenocarcinoma tends to be slow. Therefore, tumor response should be evaluated with sufficient long-term observation.

### *Quality of Life and Symptoms*

Giant tumors cause various symptoms such as cancer pain, skin ulcer, tumor bleeding, odor, fever, edema, joint range-of-motion limitation, and so on.[16] These symptoms were seen in the 3 patients in this study. Although cancer pain or tumor bleeding might be improved without tumor disappearance, other symptoms will not improve without tumor shrinkage. In our study, these symptoms abated with tumor disappearance. Skin defects, however, persisted after tumor disappearance in all patients. In patient 2, the skin defect was large during treatment, but as the tumor decreased, the defect also decreased (Figure 2E). In contrast to skin necrosis caused by radiation, the normal skin around the defect that was replaced by the tumor has the potential to regenerate. When the tumor (which inhibits regeneration of the skin) disappears, the surrounding normal skin begins to regenerate, even during RT. This phenomenon has also been observed in other normal tissue such as esophageal fistula after tumor disappearance.[17] These clinical experiences suggest that RT need not be stopped because of a skin defect. In this study, reduction of skin defect and regeneration of normal skin were observed in all patients.

One of the problems is the significance of the radical treatment for the patients with extremely poor prognosis such as the patients this study. However, all of the patients actively wished to continue the treatment, and all of the patients were delighted to see the disappearance of the huge tumor. Regarding QOL, tumor shrinkage or disappearance using the modified SIB RT is thought to yield significant merit.

### *Patient Outcomes*

The 3 patients in our study died in 5 to 7.5 months after the start of RT. It is considered that there are 2 major problems to obtain long survival in these patients. One is to control the huge locally advanced tumor, and the other is to control the small but multiple distant metastases. Long-term survival cannot be obtained without solving

both of the problems. Although long-term survival could not be obtained, the patients were considered to be 1 step closer to complete cure with control of the local tumor with modified SIB RT.

## Conclusion

Radiotherapy using the modified SIB technique for far-advanced breast cancer patients was analyzed. Although a great deal of care was required in delivering extremely high doses to the tumor, this technique enabled control of extremely large tumors that could not be controlled with conventional RT. In future, an increase in the number of patients included in the study and establishment of the technique will be required.

### *Limitations*

Although it has been more than 3 years from the start of this trial, the number of enrolled patients was 3. The number of patients with unresectable T4 breast tumor is very small, and the patients who undergo RT in that group is even less. Although the number of breast cancer patients in this trial was very small, we analyzed the patients using the limited number because the expected effect was obtained in all 3 cases.

### *Clinical Practice Points*

- Generally, patients with unresectable T4 tumor have had to chose only chemotherapy or palliative radiotherapy.
- This is the first paper that demonstrated controlled huge breast tumor by radiotherapy of >100 Gy with modified SIB technique.
- This new technique would demonstrate a possibility of curative treatment for patients with unresectable tumor who had no choice but to undergo palliative care.

## Disclosure

The authors have stated that they have no conflicts of interest.

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